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Signed Stephen Hordley

Dated 15 July 2004

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BJR/JW/PB60445

2. Patent application number
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0319150.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

4735887003
United Kingdom

4. Title of the invention

Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number *(if you know it)*

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	20
Claim(s)	2
Abstract	
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10. If you are also filing any of the following, state how many against each item.

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature B J Russell Date 14-Aug-03

12. Name and daytime telephone number of person to contact in the United Kingdom

B J Russell 01279 644398

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Novel Compounds

This invention relates to novel amide derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in medicine, especially in the treatment of various disorders.

Vanilloids are a class of natural and synthetic compounds that are characterised by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group. Vanilloid Receptor (VR-1), whose function is modulated by such compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg (The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51, No. 2.).

A wide variety of Vanilloid compounds of different structures are known in the art, for example those disclosed in European Patent Application Numbers, EP 0 347 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and International Patent Applications, Publication Numbers WO 92/09285, WO 02/100819 and WO 02/076946. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin or trans 8-methyl-N-vanillyl-6-nonenamide which is isolated from the pepper plant, capsazepine (*Tetrahedron*, 53, 1997, 4791) and olvanil or - N-(4-hydroxy-3-methoxybenzyl)oleamide (*J. Med. Chem.*, 36, 1993, 2595).

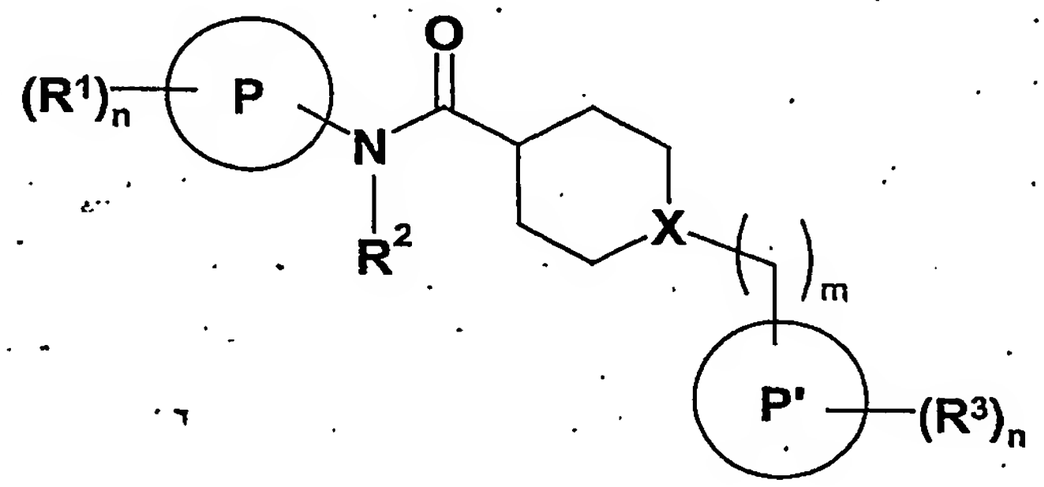
International Patent Application, Publication Number WO 02/08221 discloses diaryl piperazine and related compounds which bind with high selectivity and high affinity to vanilloid receptors, especially Type I Vanilloid receptors, also known as capsaicin or VR1 receptors. The compounds are said to be useful in the treatment of chronic and acute pain conditions, itch and urinary incontinence.

International Patent Applications, Publication Numbers WO 02/16317, WO 02/16318 and WO 02/16319 suggest that compounds having a high affinity for the vanilloid receptor are useful for treating stomach-duodenal ulcers.

International Patent Applications, Publication Numbers WO 02/072536, WO 02/090326, WO 03/022809 and WO 03/053945; and International Patent

Application Number PCT/GB03/00608 also describe a variety of compounds having activity as vanilloid receptor antagonists.

According to a first aspect of the present invention, there is provided a compound of formula (I),



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein,

P represents phenyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, benzoisoxazolyl or benzothiazolyl;

P' represents phenyl, pyridinyl or pyrimidinyl;

R^1 and R^3 may be the same or different and represent alkyl, alkoxy, halo, $-CF_3$, $-OCF_3$, -OH, =O, -CN, $-NO_2$, $-SO_2NH_2$, $-SO_2R^4$ or $-NR^4R^5$;

R^2 represents –H;

R^4 and R^5 may be the same or different and represent –H or alkyl;

m represents 0 or 1;

n represents 0, 1, 2, 3, 4 or 5; and

X represents N or CH.

Preferably, P represents phenyl. Preferably, P represents quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, benzoisoxazolyl or benzothiazolyl.

Preferably, P' represents phenyl. Preferably, P' represents pyridinyl or pyrimidinyl.

Preferably, R^1 represents alkyl, halo, =O, $-SO_2NH_2$, or $-SO_2Me$.

Preferably, R^3 represents alkyl, alkoxy, halo, $-CF_3$ or –CN.

Preferably, R^4 is –H or methyl.

Preferably, R^5 is –H or methyl.

Preferably, m represents 0. Preferably, m represents 1.

Preferably, n represents 0, 1 or 2.

Preferably, X represents N. Preferably, X represents CH.

Preferred compounds according to this invention include Examples 1 - 40 or pharmaceutically acceptable salts or solvates thereof.

Certain of the carbon atoms of formula (I) are chiral carbon atoms, and therefore compounds of formula (I) may exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of formula (I) including enantiomers and mixtures thereof, such as racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

As indicated above, the compounds of formula (I) can form salts, especially pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts are those used conventionally in the art and include those described in *J. Pharm. Sci.*, 1977, **66**, 1-19, such as acid addition salts.

Suitable pharmaceutically acceptable salts include acid addition salts.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

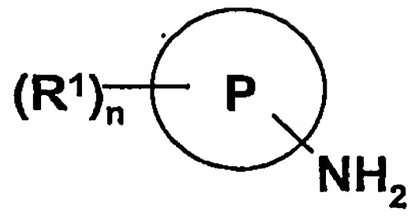
As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. The term "cycloalkyl" as part of a group refers to a saturated alicyclic hydrocarbon radical containing 3 to 12 carbon atoms, suitably 3 to 6 carbon atoms. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino. Alkyl is preferably unsubstituted.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino. Alkoxy is preferably unsubstituted.

The term "halo" is used herein to describe, unless otherwise stated, a group selected from fluorine ("fluoro"), chlorine ("chloro"), bromine ("bromo") or iodine ("iodo").

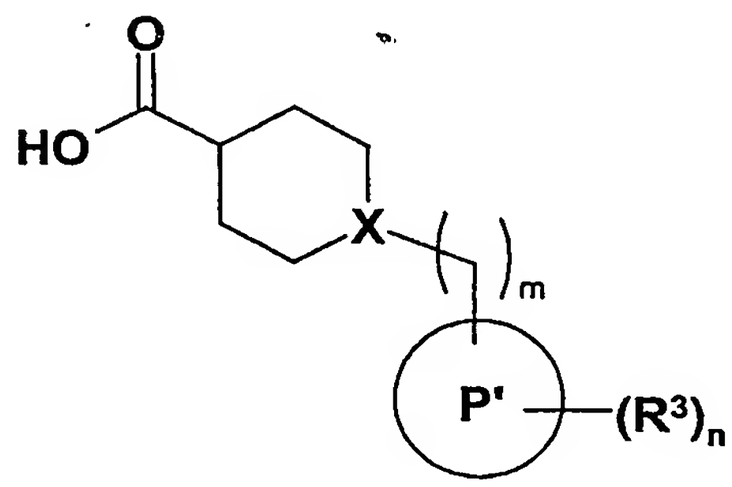
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, which process comprises:

(a) reacting a compound of formula (II),



(II)

wherein, P, R^1 and n are as defined in relation to formula (I), with a compound of formula (III),



(III)

wherein, P', R^3, m, n and X are as defined in relation to formula (I) and thereafter, as necessary, carrying out one or more of the following reactions:

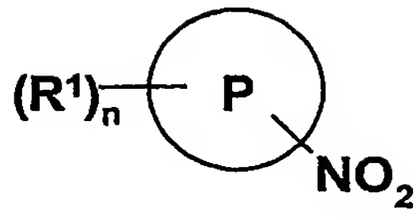
(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

The reaction between a compound of formula (II) and a compound of formula (III) may be effected using conventional methods for the formation of an amide bond, such as those described in J March, *Advanced Organic Chemistry*, 4th edition, J Wiley & Sons, 1992, p. 419-421.

Compounds of formula (II) are either commercially available, or may be prepared by the reaction of a compound of formula (IV),



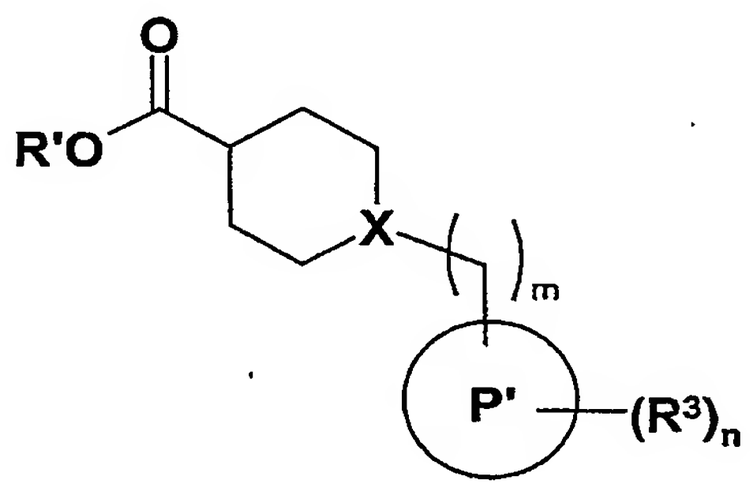
(IV)

wherein, P, R^1 and n are as defined in relation to formula (I), with a suitable reducing agent.

The reaction of a compound of formula (IV) with a reducing agent may be effected by methods well known in the art, such as those described in J March, *Advanced Organic Chemistry*, 4th edition, J Wiley & Sons, 1992, p. 1216-1218. Suitable reducing agents include (a) iron or zinc metal in hydrochloric acid, or (b) hydrogen in the presence of a suitable catalyst, such as, 5% palladium on charcoal. Reduction using hydrogen may conveniently be performed in a solvent such as methanol or ethanol..

Compounds of formula (IV) are commercially available or may be prepared according to literature methods.

Compounds of formula (III) are either commercially available or may be prepared by hydrolysis of a compound of formula (V),



(V)

wherein, P', R^3, m, n and X are as defined in relation to formula (I) and R' is an alkyl group. A suitable hydrolysis agent is aqueous hydrochloric acid. A suitable solvent is ethyl acetate.

Compounds of formula (V) are commercially available or may be prepared according to literature methods such as those described in *J. Org. Chem.* 28, 1963, 3259 or *J. Am. Chem. Soc.* 118, 1996, 7215.

The above-mentioned conversions of a compound of formula (I) into another compound of formula (I) include any conversion, which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) converting one group R^1 into another group R^1; and

(ii) converting one group R^3 into another group R^3.

The above-mentioned conversions (i) – (ii) may be performed using any appropriate method under conditions determined by the particular groups chosen.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. ' Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures known in the art.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts and solvates thereof have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain disorders, or treatment of the pain associated with them, such as: pain, chronic pain, neuropathic pain, postoperative pain, postrheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, dental pain, headache, migraine, neuropathies, carpal tunnel syndrome, diabetic neuropathy, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, neuritis, sciatica, nerve injury, ischaemia, neurodegeneration, stroke, post stroke

pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, broncho constriction, inflammatory disorders, oesophagitis, heart burn, Barrett's metaplasia, dysphagia, gastroeosophageal relux disorder (GERD), stomach and duodenal ulcers, functional dyspepsia, irritable bowel syndrome, inflammatory bowel disease, colitis, Crohn's disease, pelvic hypersensitivity, pelvic pain, menstrual pain, renal colic, urinary incontinence, cystitis, burns, itch, psoriasis, pruritis, emesis (hereinafter referred to as the "Disorders of the Invention").

Accordingly, the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance, in particular, in the treatment and/or prophylaxis of the Disorders of the Invention.

In particular, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or prophylaxis of pain.

The invention further provides a method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Disorders of the Invention, in mammals including humans, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, particularly the Disorders of the Invention.

In order to use the compounds of the invention in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus, the present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier or excipient therefor.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is

usually adapted for oral, parenteral, rectal administration or intravesical adminstration to the bladder and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions, suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01mg to 100mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend for a number of weeks or months.

No unacceptable toxicological effects are indicated with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of the compounds of the invention.

Abbreviations

DMF = Dimethylformamide

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Description 1

5-Nitro-1-methylquinolinium iodide (D1)

A mixture of 5-nitroquinoline (5 g, 0.028 mol) and iodomethane (5.4 ml, 0.086 mol) in DMF (8 ml) was heated to 40°C. After 2h a thick dark red precipitate was

formed. The reaction mixture was cooled and diluted with acetone. The solid was filtered and washed with acetone, and dried to give the title compound as an orange solid.

Description 2

5-Nitro-1-methyl-2-(1*H*)-quinolinone (D2)

5-Nitro-1-methylquinolinium iodide, (D1, 8.47 g, 0.027 mol) in warm water (90 ml) was added dropwise to a solution of potassium ferricyanide, (33.6 g, 0.1 mol) in 10% aqueous sodium hydroxide maintained at 45°C. After 5h the temperature was raised to 60°C and the solution heated for ca. 24h. The solution was cooled in an ice bath for 15 minutes and the grey-green solid filtered off, washed with water and dried. The crude solid was dissolved in a minimum amount of dichloromethane, filtered through silica gel and washed with ethyl acetate until no further product was eluted. Removal of ethyl acetate under reduced pressure afforded the title compound as a dark orange solid.

Description 3

5-Amino-1-methyl-2-(1*H*)-quinolinone (D3)

5-Nitro-1-methyl-2-(1*H*)-quinolinone, (D2, 2.59 g, 0.13 mol) in ethanol, (100 ml) and DMF (30 ml) was treated with 10% palladium on charcoal, (1 g, 50% w/w water). The reaction mixture was hydrogenated for a total of 8h at atmospheric pressure and then concentrated under reduced pressure. Trituration with ether afforded the title compound as a buff solid.

Description 4

1-(4-Chlorophenyl)piperidine-4-carboxylic acid, ethyl ester (D4)

Racemic BINAP (2.25 g, 0.0036 mol), palladium acetate (0.82 g, 3.65 mmol) and caesium carbonate (16.86 g, 0.051 mol) were suspended in 1,4-dioxane (100 ml) and sonicated for 45 minutes. 4-Bromo-chlorobenzene (5 g, 26.12 mmol) and

ethyl isonipecoacetate (4.11 g, 26.12 mmol) were added as a solution in 1,4-dioxane (100 ml). The mixture was heated to 105°C for 16h. On cooling the solvent was stripped off and the residues partitioned between water (100 ml) and diethyl ether (100 ml). The aqueous was re-extracted with ether. The combined layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (ethylacetate/pet. ether eluent) yielded the title compound as a clear yellow oil.

Description 5

1-(4-Chloro-phenyl)-piperidine-4-carboxylic acid (D5)

A solution of D4 (1.82 g, 0.0067 mol) in 1N LiOH (30 ml) and dioxane (30 ml) was stirred at room temperature for 16h and then evaporated *in vacuo*. Work up with 1M HCl and ethyl acetate gave the title compound as a yellow solid.

Example 1

1-(4-Chlorophenyl)-*N*-(1-methyl-2-oxo-1,2-dihydro-5-quinolinyl)-4-piperidinecarboxamide (E1)

A suspension of 1-(4-chlorophenyl)-4-piperidinecarboxylic acid, (D5, 150mgs, 0.63 mM) in dichloromethane, (5 ml) under argon, was treated with oxalyl chloride, (0.164 ml, 1.88 mM) and 1 drop of DMF. After 2h, the solution was concentrated under high vacuum to remove excess reagents and then redissolved in dichloromethane, (10 ml). The solution was cooled in an ice-bath and treated with a solution of 5-amino-1-methyl-2-(1H)-quinolinone, D3 (109 mg, 0.03 mmol) and pyridine, (0.061 ml, 0.75 mmol). The reaction mixture was kept at room temperature for ca. 2h, then 45°C for a further 2h and 24h at room temperature again. The thick precipitate formed was removed by centrifugation, washed with dichloromethane then ether and dried to give the title compound as a buff solid, (156mgs, 63%). MH^+ 396.

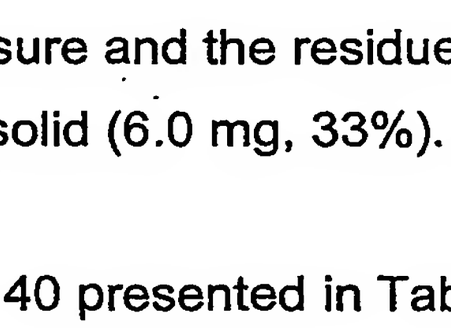
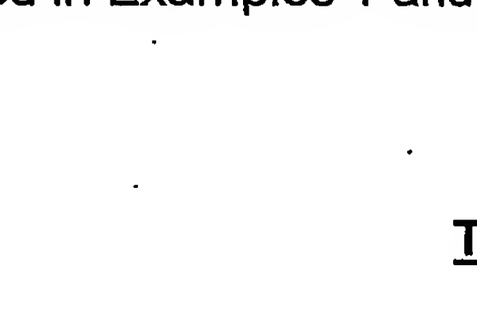
Example 2

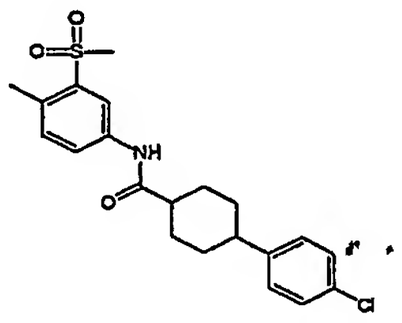
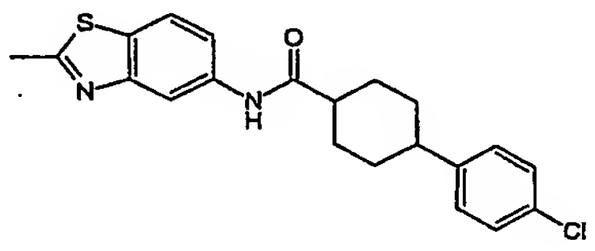
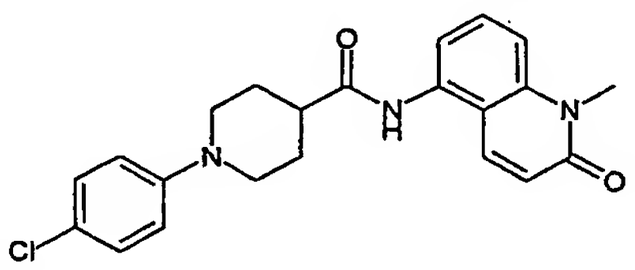
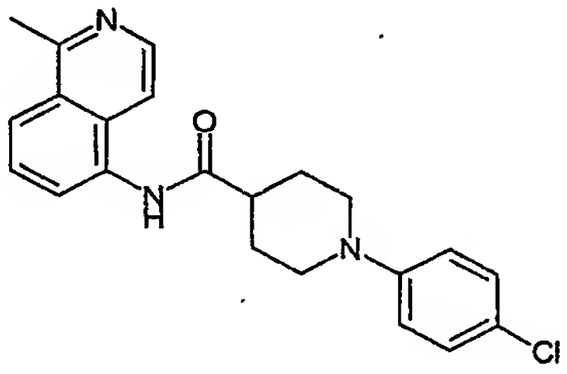
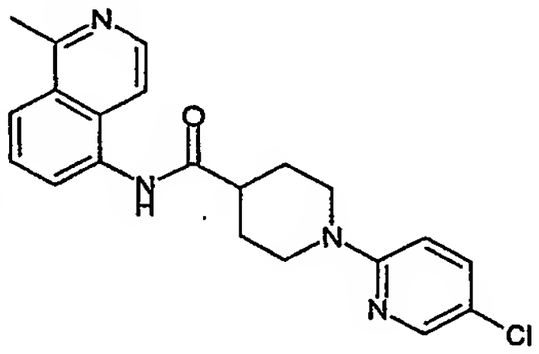
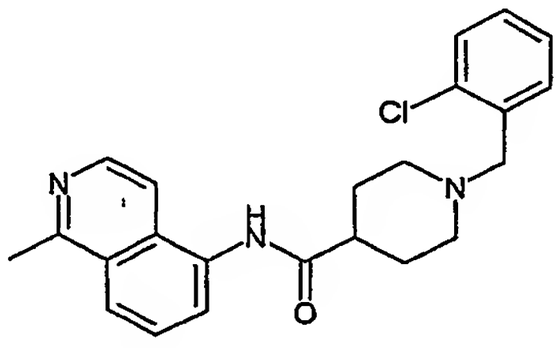
4-(4-chlorophenyl)-*N*-5-quinolinylcyclohexanecarboxamide (E2)

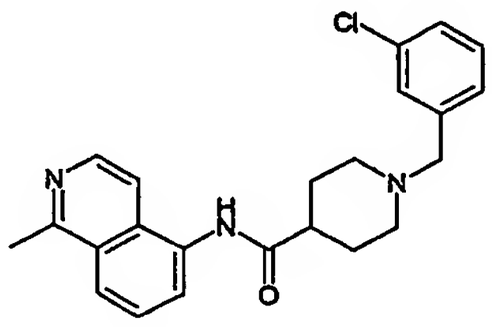
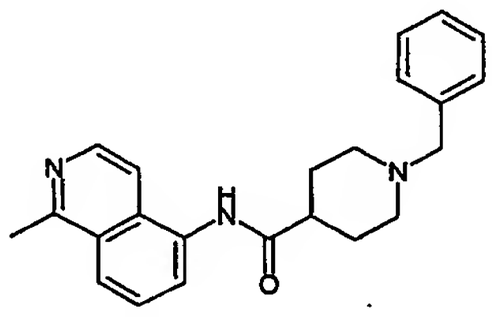
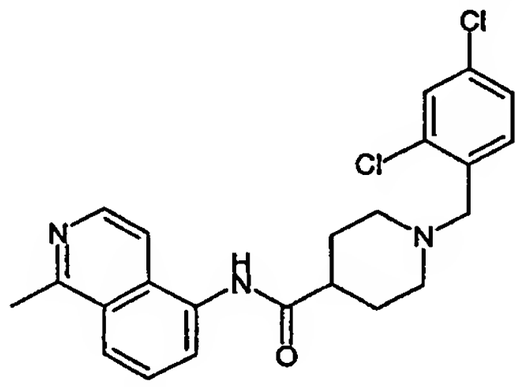
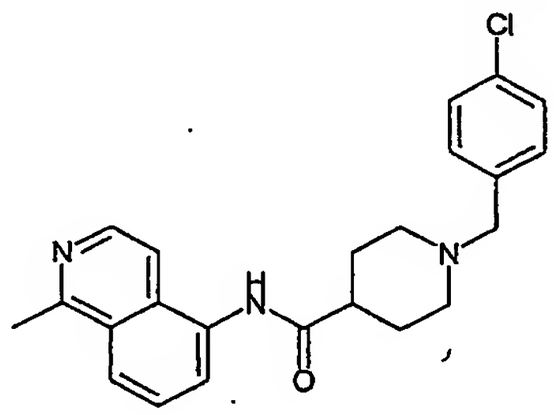
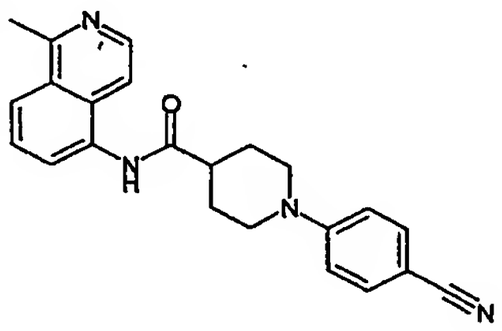
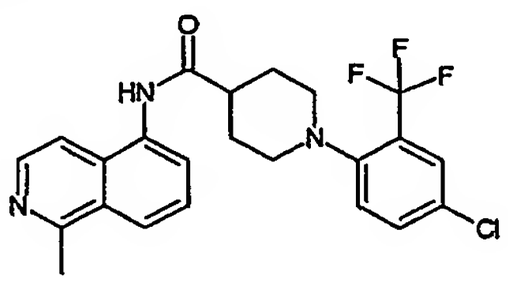
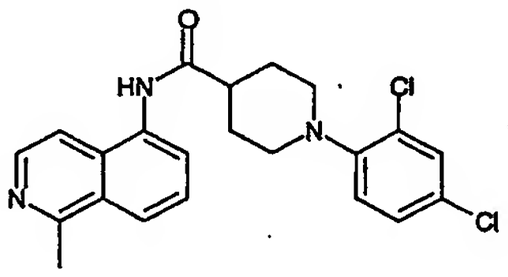
To a solution of 4-(4-chlorophenyl)cyclohexanecarboxylic acid (11.9 mg, 0.05 mmol) (Maybridge Chemical Company) in *N*, *N*-dimethylacetamide (1mL) was added thionyl chloride (2.0 M solution in CH_2Cl_2, 25 μL, 0.05 mmol) and the resulting solution was stirred for 30 minutes before 5-aminoquinoline (7.2 mg, 0.05 mmol) (Aldrich Chemical Company) and diisopropylethylamine (19 μL, 0.15 mmol) were added as a solution in *N*, *N*-dimethylacetamide (0.5 mL). The solution was then stirred for 16 hours before the solvent was removed under reduced pressure and the residue purified by reverse phase preparative HPLC to yield a white solid (6.0 mg, 33%). MH^+ = 365.

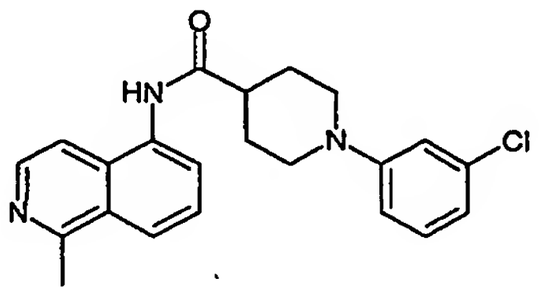
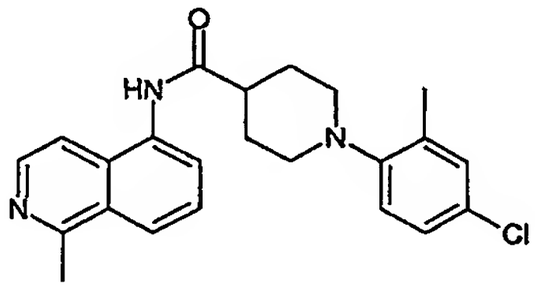
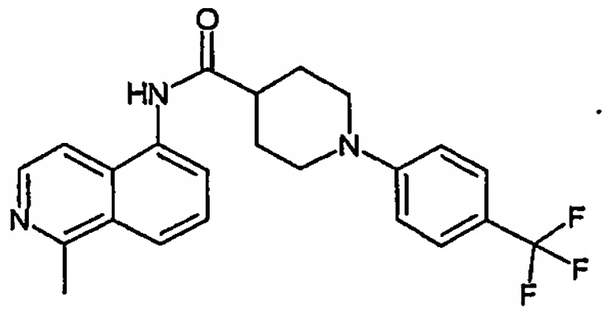
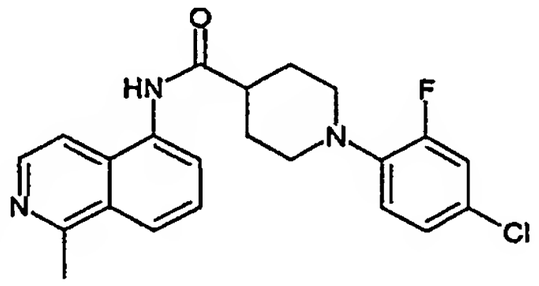
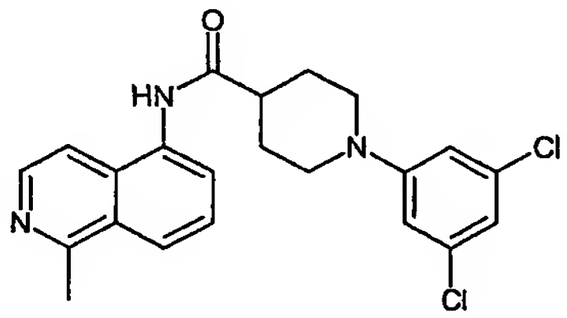
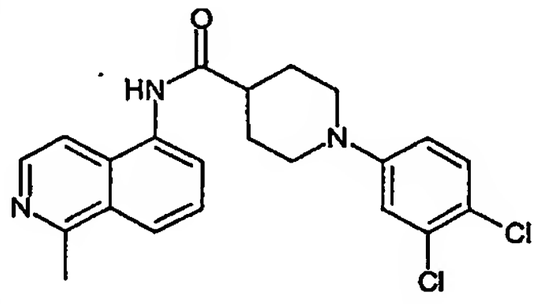
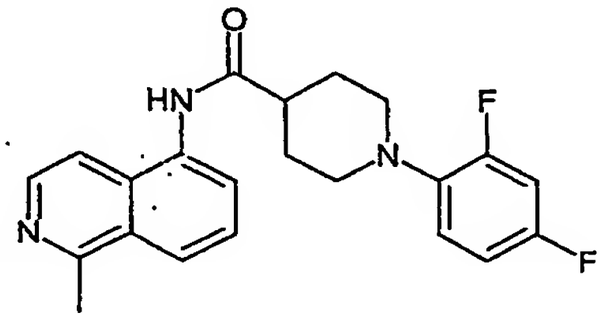
Examples 3 - 40 presented in Table 1 were prepared by analogous procedures to those described in Examples 1 and 2.

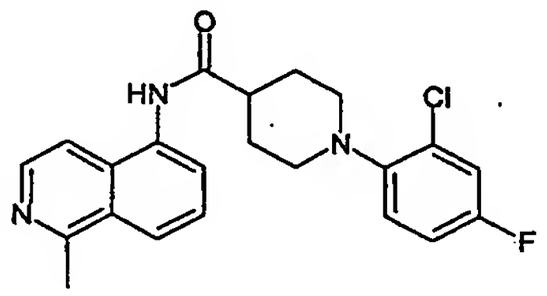
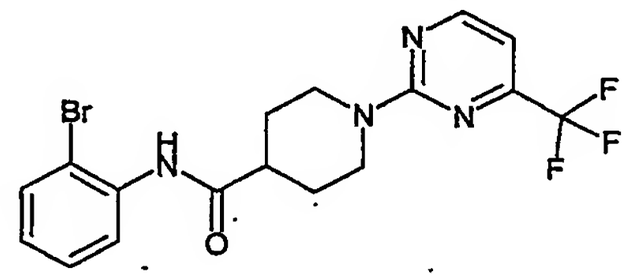
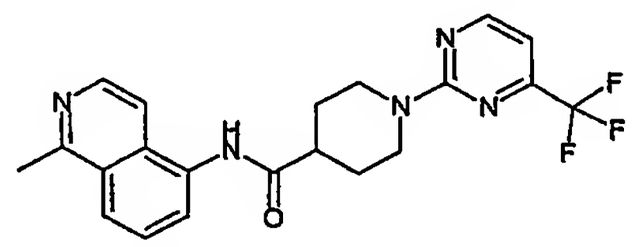
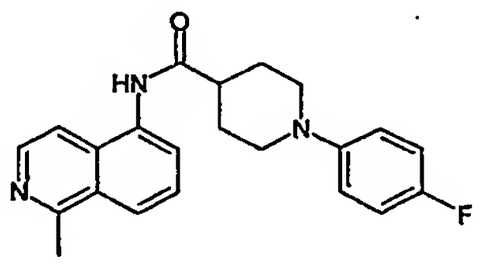
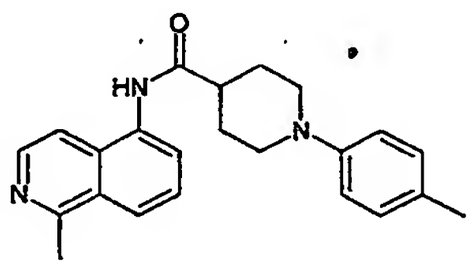
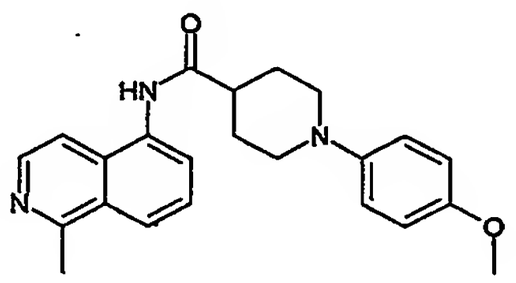
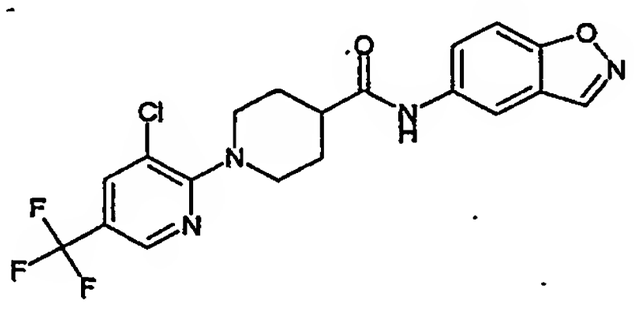
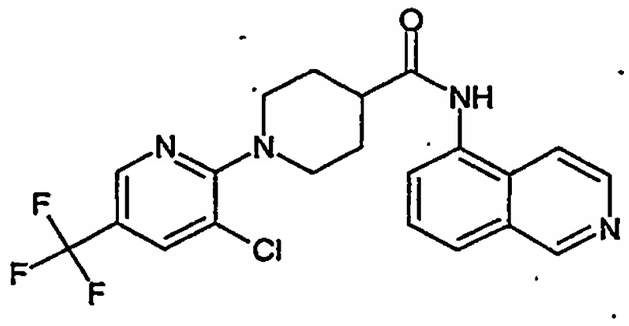
Table 1

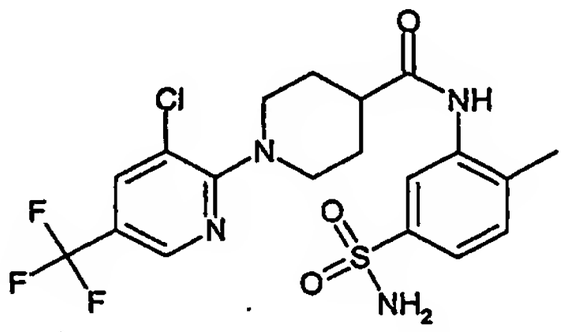
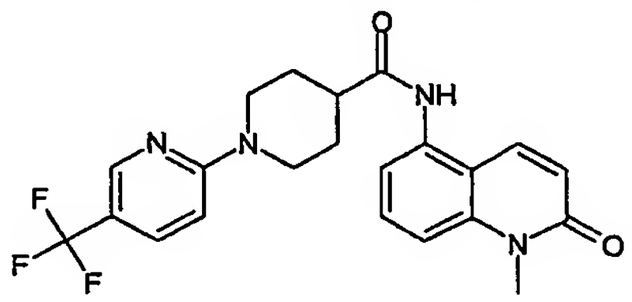
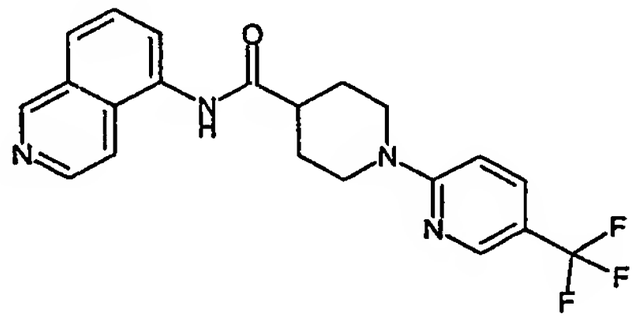
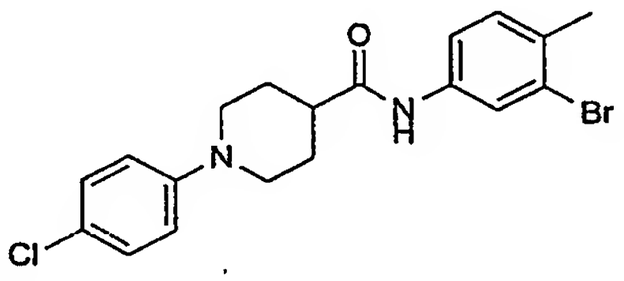
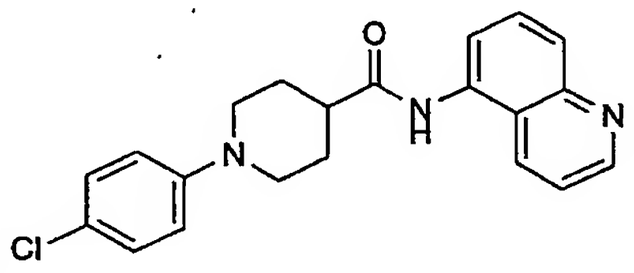
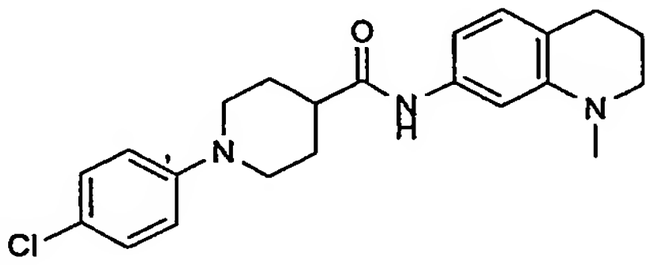
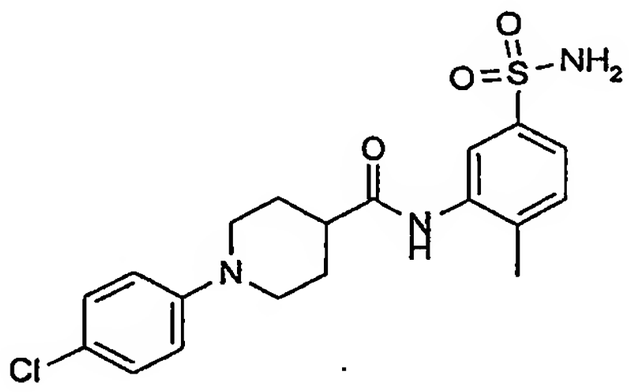
Example Number	Structure	MH+ (observed)
3		379
4		407

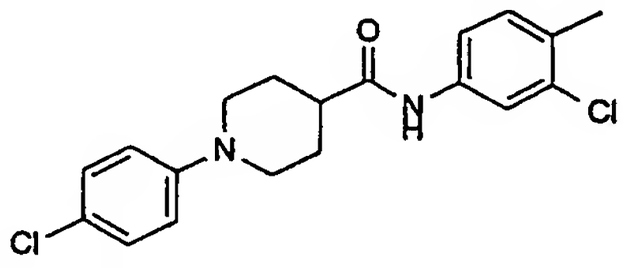
5		406
6		385
7		396
8		380
9		381
10		394

11		394
12		360
13		428
14		394
15		371
16		448
17		414

18		380
19		394
20		414
21		398
22		414
23		414
24		382

25		398
26		430
27		416
28		364
29		360
30		376
31		425
32		435

33		477
34		431
35		401
36		408
37		366
38		384
39		408

40		363

Pharmacological Data

(a) In vitro assay

As referenced above, the compounds of the invention are vanilloid receptor (VR1) antagonists and hence have useful pharmaceutical properties. Vanilloid receptor (VR1) antagonist activity can be confirmed and demonstrated for any particular compound by use of conventional methods, for example those disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W. Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts mentioned herein.

The screen used for the compounds of this invention was based upon a FLIPR based calcium assay, similar to that described by Smart et al. (British Journal of Pharmacology, 2000, 129, 227-230).

Transfected astrocytoma 1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at 25,000cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4μM Fluo-3 AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates were then washed 4 times with Tyrode containing 1.5mM calcium, without probenecid.

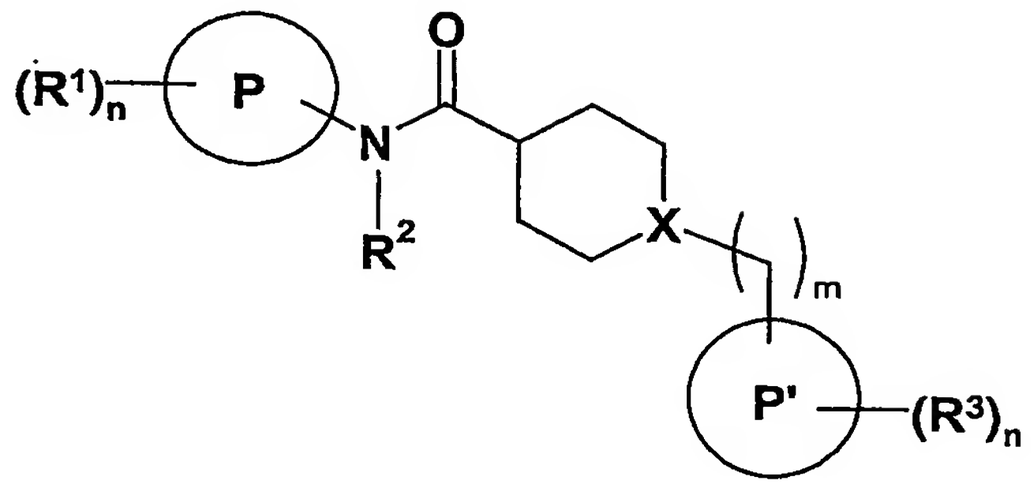
The cells were pre-incubated with compound or buffer control at room temperature for 30 minutes. Capsaicin (Sigma) was then added to the cells. Compounds having antagonist activity against the human VR1 were identified by detecting differences in fluorescence when measured after capsaicin addition,

compared with no compound buffer controls. Thus, for example, in the buffer control capsaicin addition results in an increase in intracellular calcium concentration resulting in fluorescence. A compound having antagonist activity blocks the capsaicin binding to the receptor, there is no signalling and therefore no increase in intracellular calcium levels and consequently lower fluorescence. pKb values are generated from the IC_{50} values using the Cheng-Prusoff equation.

All compounds tested by the above methodology had pKb > 6, preferred compounds having a pKb > 7.0.

Claims

1. A compound of formula (I),



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein,

P represents phenyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, benzoisoxazolyl or benzothiazolyl;

P' represents phenyl, pyridinyl or pyrimidinyl;

R^1 and R^3 may be the same or different and represent alkyl, alkoxy, halo, $-CF_3$, $-OCF_3$, -OH, =O, -CN, $-NO_2$, $-SO_2NH_2$, $-SO_2R^4$ or $-NR^4R^5$;

R^2 represents –H;

R^4 and R^5 may be the same or different and represent –H or alkyl;

m represents 0 or 1;

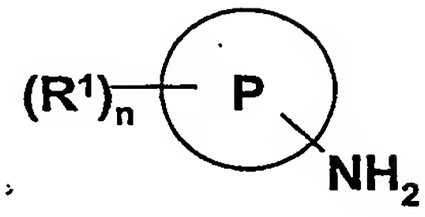
n represents 0, 1, 2, 3, 4 or 5; and

X represents N or CH.

2. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

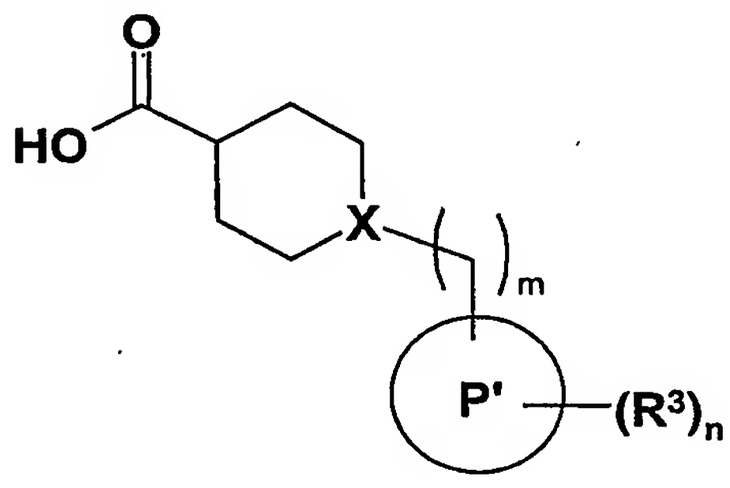
3. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, which process comprises:

(a) reacting a compound of formula (II),



(II)

wherein, P, R^1 and n are as defined in relation to formula (I), with a compound of formula (III),



(III)

wherein, P', R^3, m, n and X are as defined in relation to formula (I) and thereafter, as necessary, carrying out one or more of the following reactions:

(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

4. A pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier or excipient therefor.

5. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an active therapeutic substance.